REMARKS

This Amendment and remarks are filed in response to the Non-Final Office Action dated June 9, 2009 wherein all pending claims stand rejected.

Status of Claims

Claims 31-42, 45 and 46 are pending in the application. Claim 31 is canceled, claims 32 and 33 are amended and a new claim 46 is added.

Rejection under 35 USC § 112

Claims 31-42 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 31 recites, "wherein said anti-migraine drug is selected from the group consisting of... chlorpromazine, valproic acid, and, and wherein said anti nausea ... ". There should be an "and" between the last two groups in a Markush group (i. e., chlorpromazine, and valproic acid), and it is unclear whether more groups are intended to be listed after valproic acid since there is recited "and, and ... ".

Applicants canceled claim 31 making the rejection under 35 USC 112, second paragraph moot.

Rejections under 35 USC § 103

Claims 31-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrison et al. (US 6,197,327) in view of Hagenlocher et al. (EP 0 391 852 A2) and Jannetta (US 2002/0055495).

Examiner argues that Harrison et al., teach a method for treatment of dysmenorrhea comprising an intravaginal drug delivery system containing an appropriate pharmaceutical agent incorporated into a pharmaceutically acceptable carrier whereby the pharmaceutical agent is released into the vagina and absorbed through the vaginal mucosa to provide relief of dysmenorrhea (abstract). Harrison et al. further teach the pharmaceutically acceptable carrier comprises a hydrophilic or hydrophobic carrier, such as semi-synthetic glycerides of saturated fatty acids with 8 to 18 carbons and PEG 6000/1500, respectively, (column 8, lines 8-15). Also, Harrison et al. teach the pharmaceutical formulations further comprising a mucoadhesive agent, preferably hydroxypropyl methylcellulose (column 8, lines 16-22), and a penetration enhancer, preferably ethoxydiglycol (column 8, lines 23-28). Harrison et al. also teach the method of applying the pharmaceutical formulation with the aid of an intravaginal delivery device, such as tampon device, vaginal ring, pessary, tablet, vaginal

suppository, vaginal sponge, bioadhesive tablet, bioadhesive microparticle, cream, lotion, foam, ointment, solution and gel (column 2, lines 37-43; column 3, lines 8-67; column 4, lines 1-27; and column 9, line 4 through column 13, line 67). Harrison et al., also teach that preferred formulations for hydrophilic drugs comprise between about 60-90% by weight lipophilic carrier, between about 5-25% mucoadhesive agent, and between about 5-20% sorption promoter, whereas preferred formulations for lipophilic drugs comprise between about 50-90% by weight hydrophilic carrier, between about 5-20% mucoadhesive agent, and between about 5-25% sorption promoter (column 8, lines 31-34 and 44-47). Harrison et al., further teach that the drug delivery systems treat or prevent dysmenorrhea, and alleviate and prevent painful menstruation and symptoms such as nausea, fatigue, diarrhea, lower backache, and headache (col. 12, lines 14-20).

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to incorporate anti-nausea drugs, such as metoclopramide, into the formulations of Harrison et al., because Hagenlocher et al., teach that vaginal therapy is an effective systemic treatment, and both Hagenlocher et al., and Jannetta teach that anti-nausea drugs can be administered as suppositories.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Examiner then discusses Applicants argument on page 12 that the aim of Harrison et al., is to deliver the needed amount of the drug to the uterus but limit the concentration of the drug in the systemic circulation. However, the Examiner respectfully argues that Harrison et al., teach that the intravaginal delivery results in a reduction of first-pass metabolism in the liver by avoiding the gastrointestinal system, which in turn results in a reduction of side effects due to lower systemic concentrations (col. 5, line 58 through col. 6, line 2). The Examiner contends that Harrison et al. teach one of ordinary skill in the art that intravaginal administration of a drug bypasses first-pass metabolism in the liver by avoiding the gastrointestinal tract, and therefore has a reduction in side effects. Also, in combination with Hagenlocher et al. and Jannetta, it is obvious that intravaginal delivery of anti-emetic drugs can sufficiently treat nausea. Also, US 6,572,874 teaches intravaginal delivery systems (suppositories) comprising the three basic components: glycerides of saturated fatty acids having eight to eighteen carbons (SUPPOCIRE®), HPMC and ethoxydiglycol

(TRANSCUTOL®); wherein the suppositories resulted in systemic circulation of the drug in concentrations ten to thirty times higher than those delivered orally (col. 5, lines. 59-67; and col. 27, lines. 37-43). Therefore, the intravaginal delivery system of Harrison et al., is taught to result in systemic circulation.

Applicants disagree. First, the cited reference, Harrison '327, does not correspond, in some instances, to cited columns and lines. Did Examiner mean Harrison 6,086,909 or Harrison 6,572,874. Second, claims have now been amended to be directed to a method for a rapid onset of systemic treatment of migraine and migraine headache, nausea and vomiting, by pulsed drug delivery of an anti-migraine or anti-nausea drug into a systemic circulation where the pulsed drug delivery of is at least 6 times faster than the oral delivery. This is supported in the specification on page 26, lines 7-14 where the second peak (line 8) in the plasma concentration of sumatriptan and metoclopramide is observed and described as being a pulsed delivery (line 11). Additionally, the peak drug levels are observed within several minutes (see Figure 1 and Figure 2A and 2B) implying the rapid onset of the pharmacological activity (page 26, lines 1-6) of these drugs when formulated and administered according to the invention. The drug delivery is at least 6 times faster than oral delivery, as seen in Tables 1 and 2, where the vaginal delivery results in rapid onset of the drug released from the vaginal suppository (t_{max} min 15 minutes) compared to (t_{max} 100 minutes) for orally administered sumatriptan and vaginal release (t_{max} min 10 minutes) compared to (t_{max} 60 minutes) for orally administered metoclopramide (Tables 1 and 2).

No reference cited by Examiner or known to applicants teaches the delivery of anti-nausea or anti-migraine drug in rapid pulsating manner resulting in at least six times faster drug release and extended presence of the drug in plasma. The new claims are supported on pages 25-30, particularly in Tables 1 and 2 and Figures 1-3.

Returning to Examiner's rejection over Harrison et al., Applicants maintain that Examiner is considering the two methods, each for treatment of different pathological conditions, using different means and different site of action, to be the same or almost the same. To understand the difference between these two methods, a short summary of underlying medical and pathological conditions is necessary.

Harrison's method is for treatment of dysmenorrhea, a painful condition of the uterus. The treatment of dysmenorrheal requires delivery of the analgesic drug into uterus, thereby eliminating need for dosing a patient with large doses of the analgesics orally or parenterally. The instant invention is for treatment of migraine, painful chronic headache, and nausea, condition associated with vomiting. Both migraine and nausea are centrally

controlled by brain and require delivery of the drugs into brain by way of systemic circulation.

Dysmenorrhea is a medical condition characterized by severe uterine pain during menstruation. Dysmenorrhea is diagnosed when the pain or cramps during menstruation are so severe that medication is required. Additionally, secondary dysmenorrhea is diagnosed when symptoms are attributable to an underlying disease, disorder, or structural abnormality of the uterus, such as endometriosis (abnormalities in the lining of the uterus), adenomyosis (nonmalignant growth of the endometrium into the muscular layer of the uterus), pelvic inflammatory disease, uterine fibroids, cervical narrowing, uterine malposition or pelvic tumors.

Migraines are chronic headaches that can cause significant headache pain for hours or days. Migraine symptoms typically include severe pain often accompanied by nausea, vomiting, and extreme sensitivity to light and sound. The pain may be confined to one or both side of the head with a pulsating or throbbing in temples. When untreated, one episode of the migraine typically lasts from four to 72 hours, often with several times a month frequency.

Nausea is the sensation of unease and discomfort in the upper stomach and head with an urge to vomit. Nausea is not a sickness, but rather a symptom of several conditions, many of which are unrelated to the stomach. Nausea is often indicative of an underlying condition elsewhere in the body. Motion sickness, which is due to confusion between perceived movement and actual movement, is an example: the sense of equilibrium lies in the ear and works together with eyesight. When these two "disagree" about the extent to which the body is actually moving, the symptom is presented as nausea, although the stomach itself has nothing to do with the situation. The stomach's involvement comes from the brain's interference where the brain induces vomiting in response to some stimulus.

Consequently, both the migraine and nausea need to be treated with anti-migraine and anti-nausea drugs systemically. Delivery to the uterus with some spill over to the systemic circulation would not treat these conditions. The invention claimed herein provides for a rapid onset systemic delivery of the anti-migraine and/or anti-nausea drugs by way of vaginal delivery of these drugs into the systemic circulation in extended and pulsating manner. Such delivery provides several benefits.

Since the migraine is almost always accompanied by vomiting, the treatment with orally administered drugs is inefficient because the ingested drug is vomited. Parenteral

administration of drugs by injection is inconvenient and unpleasant, typically requiring visit to the doctor office.

The vaginal administration does not require injections, can be conveniently administered at home by the patient, has a rapid onset, long lasting effect and overall requires smaller amount of the drug than oral administration where the large portion of the drug is deactivated in liver and in GI tract. Using the method of invention, the drug is conveniently delivered into the circulation without unpleasantness and impracticality of the parenteral delivery by injections.

However, to achieve this result, the anti-migraine and/or anti-nausea drug must be delivered into the systemic circulation in sufficient dosages, quickly and with longer lasting therapeutic effect according to the invention. To deliver the majority of the drug into the uterus with some spillover getting into the systemic circulation would not treat migraine or nausea.

Therefore, while the method seems to be similar to Harrison et al., it cannot be obvious from teaching of Harrison because the treated conditions are different, the sites of the treatment are different, the drugs to treat these conditions are different, the onset of the drug delivery is different and the amount of the drug in the plasma and its lasting effect is also different.

Examiner argues that Harrison et al teaches that symptoms like nausea as a result of dysmenorrhea are treated with their intravaginal drug delivery systems. Applicants disagree. The nausea allegedly treated with Harrison intravaginal drug delivery is an associated symptom of dysmenorrhea and therefore, when the dysmenorrhea is treated with Harrison's treatment, nausea and headache will disappear naturally because the underlying condition for these symptoms is treated, not as a consequence of the Harrison treatment. Nowhere Harrison et al., discloses that their method would be suitable for treatment of migraine or nausea as such. These symptoms are eliminated only as a result of a successful treatment of dysmenorrhea.

Instant claims are not obvious from teachings of Harrison et al. Examiner then combines the Harrison reference with Hagenlocher et al reference by arguing that Harrison et al. teach that symptoms such as nausea as a result of dysmenorrhea are treated with their intravaginal drug delivery systems, but they do not teach using the instantly claimed anti-migraine or anti-nausea agents. However, Examiner continues, Hagenlocher et al., teach that a plurality of medicines are suitable for rectal or vaginal therapy with the aim of making the medicines absorb systemically or in order to achieve an effect locally in the rectum or the

vagina (page 2, lines. 3-6). Examiner maintains that Hagenlocher et al., teach a composition for rectal or vaginal application of drugs comprising at least one hydrocolloid, effective substance(s), and possibly further carrier substances; wherein said compositions are used in systemic or local therapy for rectal or vaginal application (Abstract; page. 2, lines. 44-46; and page 3, lines. 26). Hagenlocher et al. teach that effective substances include anti- emetic agents, such as metoclopramide, anti-epileptic agents, such as valproic acid, and neuroleptic agents, such as promethazine and chlorpromazine (page 3, lines. 30-49); the hydrocolloid includes hydroxypropylmethyl cellulose (page 4, lines 22-37); and carrier substances include polyethylene glycol (page 4, lines 43).

Applicants disagree. Upon careful review of Hagenlocher, et al., it becomes evident that the Hagenlocher concerns a composition for rectal and vaginal application of drug. The composition is characterized as being substantially free of fat and containing an effective substance, and at least one hydrocolloid that will effects disintegration of the applied formulation (Abstract).

Hagenlocher is cited by Examiner as disclosing a plurality of medicines suitable for rectal or vaginal therapy with the aim of making the medicines absorb systemically or in order to achieve an effect locally in the rectum or the vagina (pg. 2, lines 3-6). That is generally true, however, just the fact that there is no distinction between the rectal and vaginal delivery speaks against making the instant claims obvious. Applicants' invention and claims are directed solely to the vaginally deliverable composition into systemic circulation of anti-migraine and anti-nausea drugs where the drugs are delivered fast with rapid onset, delivery results in pulsating release of the drug from the vaginal device and have a long lasting effect. All these are supported by experimental evidence. While all kinds of drugs are mentioned as being deliverable using Hagenlocher capsules, anti-migraine drugs are not among them and rapid onset and pulsating delivery are also not taught.

Hagenlocher et al. teach a composition for rectal or vaginal application of drugs comprising at least one hydrocolloid, effective substance(s), and possibly further carrier substances. The compositions are used in systemic or local therapy for rectal or vaginal application (page 2, lines 44-46). The composition is filled into capsules or capsules with a hard casing, such as pharmaceutical hard or soft capsules made from hydrophilic polymers, i.e. starch capsules (page 2, lines 49-55 and page 3, line 26). The composition is solid and exist in granular or powder form (page 3, lines 6-8) and is filled into rounded-off capsules

coated with lubricant coats (page 3, lines 2-5). The composition further contains the effective substance mixed with swelling material and auxiliary agents (page 3, lines 17-21).

Hagenlocher et al., thus does not teach the instant method for delivery of anti-migraine and anti-nausea drugs whether combined with Harrison et al., or not.

Examiner further combines the above two references with Jannetta and argues that Jannetta teaches suppositories for the treatment of nausea and vomiting, wherein the suppositories are optionally administered in the vagina and comprise metoclopramide ([0013]-[0018]). Jannetta also teaches that the metoclopramide is administered in a dosage of about 10 to about 20 mg twice or thrice a day ([0016]).

Applicants disagree. Jannetta provides, in general, a composition comprising a combination of a steroid dexamethasone and metoclopramide that has anti-emetic effects. The composition is suitable for parenteral, oral or inhalable administration. In some instances, suppositories are provided comprising a combination of the two drugs that can be inserted into rectum or vagina or otherwise administered enterally across patient's mucosal membrane as a suppository. There is nothing in this invention that would, whether combined with Harrison et al., and/or Hagenlocher et al., make this invention obvious.

Claims 31-42 and 45 are further rejected under 35 U.S.C. 103(a) as being unpatentable over Harrison et al. (US 6,197,327) in view of Mahashabde et al. (US 2003/0133977) and Penkler et al. (US 6,255,502).

Examiner argues that Harrison et al., teach a method for treatment of dysmenorrhea comprising an intravaginal drug delivery system containing an appropriate pharmaceutical agent incorporated into a pharmaceutically acceptable carrier whereby the pharmaceutical agent is released into the vagina and absorbed through the vaginal mucosa to provide relief of dysmenorrhea (abstract). Harrison et al. further teach the pharmaceutically acceptable carrier comprises a hydrophilic or hydrophobic carrier, such as semi-synthetic glycerides of saturated fatty acids with 8 to 18 carbons and PEG 6000/1500, respectively (column 8, lines 8-15). Also, Harrison et al. teach the pharmaceutical formulations further comprising a mucoadhesive agent, preferably hydroxypropylmethylcellulose (column 8, lines 16-22), and a penetration enhancer, preferably ethoxydiglycol (column 8, lines 23-28). Harrison et al., also teach the method of applying the pharmaceutical formulation with the aid of an intravaginal delivery device, such as tampon device, vaginal ring, pessary, tablet, vaginal suppository, vaginal sponge, bioadhesive tablet, bioadhesive microparticle, cream, lotion, foam, ointment, solution and gel (column 2, lines 37-43; column 3, lines 8-67; column 4, lines 1-27; and column 9, line 4 through column 13, line 67). Harrison et al., also teach that

preferred formulations for hydrophilic drugs comprise between about 60-90% by weight lipophilic carrier, between about 5-25% mucoadhesive agent, and between about 5-20% sorption promoter, whereas preferred formulations for lipophilic drugs comprise between about 50-90% by weight hydrophilic carrier, between about 5-20% mucoadhesive agent, and between about 5-25% sorption promoter (column 8, lines 31-34 and 44-47). Harrison et al., further teach that the drug delivery systems treat or prevent dysmenorrhea, and alleviate and prevent painful menstruation and symptoms such as nausea, fatigue, diarrhea, lower backache, and headache (column 12, lines 14-20).

Harrison et al., teach that symptoms such as headache as a result of dysmenorrhea are treated with their intravaginal drug delivery systems, but they do not teach using the instantly claimed anti-migraine or anti-nausea agents. However, Mahashabde et al., teach methods for treating migraine headaches through intravaginal delivery of selected serotonin reuptake inhibitors (SSRIs) to the systemic circulation (Abstract). Mahashabde et al., teach that the intravaginal delivery results in decreased side effects due to decreased serum concentration and/or reduced first pass metabolism ([0028]). Mahashabde et al., further teach that the intravaginal composition may be formulated with a variety of pharmaceutical carriers, such as polyethylene glycols, amenable for administration as creams, gels, foams, tablets, suppositories and pessaries ([0034]). Also, Penkler et al., teach that anti-migraine drugs, such as sumatriptan, naratriptan, almotriptan, zolmitriptan, rizatriptan and eletriptan (col. 7, lines 45-48), are suitable for delivery to the vagina, such as in the form of a suppository (col. 13, lines 1-30). Therefore, it was well-known at the time of the invention to treat migraine headaches systemically through intravaginal application of anti-migraine drugs.

Examiner, therefore, concludes that it would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to administer an anti-migraine drug, such as sumatriptan, naratriptan, almotriptan, zolmitriptan, rizatriptan and eletriptan, intravaginally in the formulation of Harrison et al., because it was well-known at the time of the invention to treat migraine headaches systemically through intravaginal application of anti-migraine drugs.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicants disagree. As already stated above, Applicants amended claims to include limitations that are not and cannot be obvious from the cited prior art. No prior art made any disclosures regarding a rapid onset delivery of the anti-migraine or anti-emetic drug in pulsating manner, nor it shown any results that it would be able to achieve such results. Applicants did so and present the actual experimental data to support their claims.

The rejections should be withdrawn and the amended claims should be allowed.

SUMMARY

In summary, claims are amended and arguments are provided to overcome advanced rejections under 35 USC 112, second paragraph and under 35 USC 103. It is believed that all claims are in conditions for allowance. Notice of Allowance is respectfully requested.

Respectfully submitted,

PETERS VERNY, LLP

Dated: December 8, 2009

By _____
Hana Verny, Reg. No. 30,518
Tel.: (650) 324-1677
Fax: (650) 324-1678

PETERS VERNY, LLP
425 Sherman Avenue, Suite 230
Palo Alto, CA 94306
Customer No.: 23308